Wirefree Electrochemistry for Enhanced Detection and Treatment of Disease

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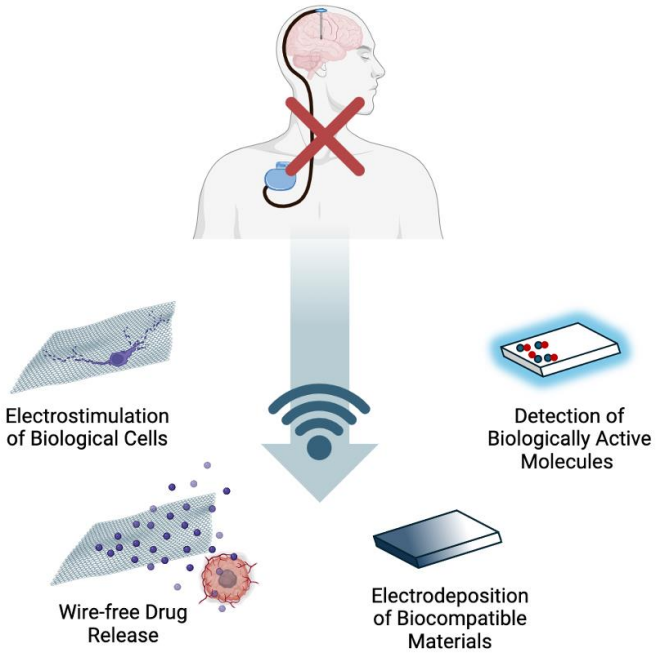

ABSTRACT: Wirefree, or bipolar electrochemistry, BPE, has the potential to transform patient outcomes through early diagnosis using ultrasensitive sensors for multiple biomarkers and personalised treatments such as enhanced cell growth, differentiation and destruction as well as local delivery of therapeutics. We highlight the emerging field of wirefree electroceuticals and show how BPE could enable precise modulation of neural circuits, non-pharmaceutical therapies for conditions like Parkinson's disease and chronic pain management, as well as on-demand drug delivery with high spatial and temporal precision. Moreover, it explores the integration of advanced nanomaterials illustrating their pivotal role in enhancing electrode performance and biocompatibility, thereby maximising their potential diagnostic and therapeutic efficacy especially *in vivo*.

1. INTRODUCTION: Electrochemistry enables many aspects that are central to contemporary, personalised, healthcare from the detection of disease biomarkers at ultralow concentrations (sub-pM),[1] to the electrical stimulation of biological cells to block Parkinson's Tremor as well as enhancing cell proliferation, differentiation, interconnection and selective destruction.[1,2,3,4,5,6] For certain diseases and conditions, e.g., the control of epileptic seizures, Parkinson's tremor, incontinence, chronic pain, cancer, hypertension, cerebrovascular and pulmonary diseases, electroceuticals represent a powerful alternative to the challenges and costs (≈€10bn) of developing a new active pharmaceutical ingredient (API) and bringing it successfully through clinical trials. However, traditional electrochemical approaches typically use physical wires to connect a working electrode or sensor to a potentiostat or power supply. This "wired" approach can make it challenging to create wearable or implantable devices, e.g., the highly successful deep brain stimulation electrodes used for Parkinson's tremor require wires from the brain to a power pack and waveform generator implanted in the chest, a significant invasive *additional* procedure which can cause persistent complications. The incidence of either hardware or bio-related *in-vivo* complications occurring post-therapy can be as high as 30-40%.[7] Common hardware-related complications include migration, fracture and failure of wired components which can damage the surrounding tissues and cellular microenvironment. Moreover, the number of electrodes (stimulation locations) is limited in part due to the challenge of wiring large numbers of electrodes. These issues could be reduced using bipolar electrochemistry since the *implanted* physical infrastructure, wiring, batteries, charging system etc., is substantially reduced or removed entirely. From a disease detection and diagnosis perspective, it is increasingly clear that for most conditions, *multiple* analytes must be quantified simultaneously to achieve the required clinical sensitivity (true positive rate, probability of a positive test result for a positive individual) and specificity (true negative rate, probability of a negative test result for an individual who is actually negative). However, this can be very challenging when each sensor must be individually wired to an independently controllable potentiostat/power supply. In contrast, BPE allows the potential of individual elements within an array of electrodes to be controlled independently, e.g., by changing their length, in a manner that is scalable in terms of the number of electrodes.

Poor patient health outcomes and low quality of life continue to challenge people with neurological issues such as Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis (ALS) including cognitive decline, premature death and high rates of institutionalisation care.[8] The primary factors which contribute to poor patient prognosis in neurological disorders include the complexity of the central nervous system (CNS) and brain neural network, the degenerative nature of the disease, lack of distinctive biomarkers and effective diagnostic techniques and an incomplete understanding

of disease mechanisms at the cellular level.[9,10,11,12,13] As a result, many approaches are currently focused on treating symptoms treatments rather than the underlying pathophysiology.[14] The burgeoning field of *wired* electroceuticals has significantly improved the quality of life for patients suffering from chronic pain, muscle damage and combating involuntary movement disorders such as tardive dyskinesia, akinesia and dystonia.[15] Electroceuticals use electrical/electrochemical impulses to stimulate cells locally and can be applied to neuronal/nerve cells as well as cardiac, smooth muscle, and mitotic cells. Recent work suggests that all cells may respond to electrical/electrochemical stimuli most likely linked to their resting membrane potential. Therefore, there may be broad scope to use electroceuticals for cell manipulation, e.g., stimulated growth and differentiation, and stimulation through electrical, electrochemical and active pharmaceutical ingredients delivered using electrically driven drug delivery systems.[16]

2. Mechanism of Wirefree Electrical and Electrochemical Stimulation: As illustrated in Figure 1, in wirefree or bipolar electrochemistry, a voltage difference is applied to two or more feeder or drive electrodes by connecting them to an external DC or AC power source to generate an electric field within a (biological) sample, an array of biological cells or tissue. The simplest configuration involves a pair of feeder electrodes placed perpendicularly a short distance from either end of a horizontal bipolar electrode. Under ideal conditions, the electric field through the solution would decay approximately linearly causing a linear change in the potential induced in the bipolar electrode along its length.[17] The magnitude of the voltage induced within the bipolar electrode is determined by the local electric field strength (controlled by the voltage difference applied to the pair of drive electrodes), the separation between the feeders, the physical size of the bipolar electrode and the concentration of the supporting electrolyte. The bipolar electrode acts as a complete electrochemical cell and, if the induced potentials are sufficient, oxidation can occur at one end, or pole, of the bipolar electrode and reduction at the other with the electrons transferred being balanced.[18] One challenge of this electrode configuration is that the current cannot be easily measured directly, but this issue can be solved by more sophisticated configurations. For example, a pair of split BPEs linked by an ammeter or linking the current flow to electrochemiluminescence. As shown in Figure 2, the potential distribution through the solution is rarely truly linear,[2] e.g., when an electrolyte is present (almost inevitable for biological samples) the electric field strength will decrease essentially exponentially close to the feeder electrodes leaving only a fraction of the field available to induce voltages within the working bipolar electrode. Therefore, to achieve the required electric field strength in solution that will induce the potential needed to drive an electrochemical process of interest, the voltage applied to the feeder electrodes will have to be increased. This increased voltage, potentially several hundred volts depending on the size of the bipolar electrode and the electrolyte concentration, can

cause significant challenges in terms of corrosion of the feeder electrode that is positively biased. An alternating AC voltage can also be applied[3] or, similar to wireless phone charging, an alternating magnetic field can be used to wirelessly induce a voltage in a remote coil and if electrodes are connected to either end, redox reactions can be driven wirelessly.

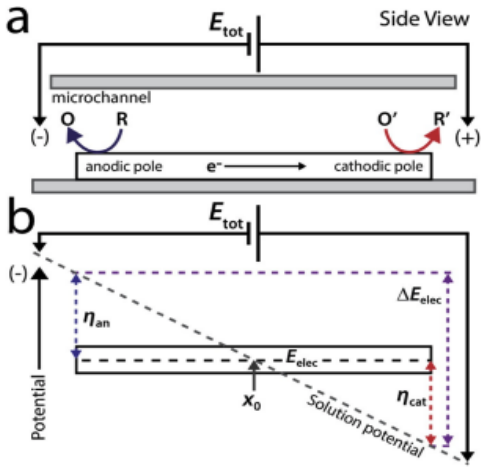

Figure 1. a) *Side-view schematic representation of bipolar inherent dual redox capabilities. A planar BPE placed between two feeder electrodes with specific voltage potentials leads to distinct redox reactions occurring at the poles of the BPE structure. Oxidation of the solution species occurs at the anodic pole whereas simultaneous reduction of the solution species is experienced at the cathodic pole.* ***b)*** *Schematic illustration of the electric field-induced gradient overpotential across the BPE surface. The highest potentials are observed at the poles i.e. site of redox reactions. A depletion zone of which no overpotential is observed is depicted at the midpoint of the BPE however the nature of the faradaic reactions impacts the exact location of this zero potential boundary for each BPE. Reproduced from Crooks, R. M. Principles of Bipolar Electrochemistry. ChemElectroChem* ***2016****, 3 (3), 357–359. DOI:10.1002/celc.201500549.*

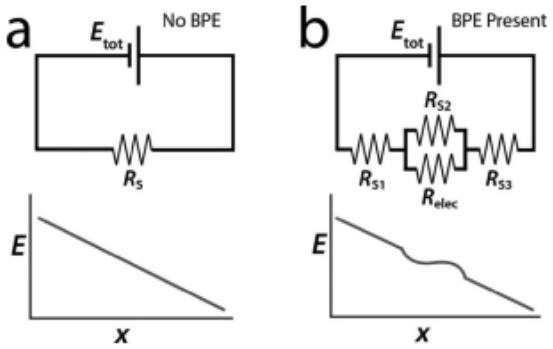

Figure 2. a) *Circuit diagram and potential distribution plot showing an ionic current mediated linear decay in potential across the feeder terminated bipolar cell.* ***b)*** *Circuit diagram and potential distribution plot showing a modulated potential distribution across the BPE surface between both poles*

of the BPE through which electrons can move. Reproduced from Crooks, R. M. Principles of Bipolar Electrochemistry. ChemElectroChem ***2016****, 3 (3), 357–359. DOI:10.1002/celc.201500549.*

Achieving a homogeneous electric field depends strongly on the geometry of the system, e.g., using a bipolar electrode that is narrower than the feeders, or placing it too close to either feeder, can cause inhomogeneities, especially at the edges of the bipolar electrode. Transport mechanisms beyond diffusion also need to be considered. Typically, at least one oxidation state is charged, and any charged species can migrate in the electric field, with Ox and RED possibly moving in different directions, especially when the electrolyte concentration is low. Moreover, current flow through the BPE can change the induced potential locally. These effects can alter faradaic processes ranging from electrochemiluminescence intensity to analyte detection sensitivity and thicker deposits of conducting polymers.

3. Detection of Biologically Active Molecules. Measuring the current flow through a bipolar electrode, e.g., in response to the binding of a redox-active target or the binding of a probe strand or secondary antibody labelled with a redox-active probe, generally requires a more complex geometry, e.g., a split bipolar electrode with the two sections bridged by a high impedance ammeter. This challenge has led to a significant increase in wireless electrochemiluminescence (ECL) detection where the light intensity depends on the concentration of the target analyte.[4,5] Significant progress has been made for selective and sensitive (multi-)analyte detection including new luminophores and co-reactants as well as the optimisation of the cell geometry, e.g., miniaturised cells for applications where the sample volume is restricted.[6,19,20,21] The key advantages of ECL, i.e., a high signal-to-noise ratio due to a dark background leading to low limits of detection, high analytical sensitivity, wide dynamic range, simplified instrumentation since a calibrated light source is not required and short sample-to-answer times, are preserved, while the bipolar approach enables multianalyte analysis at independent electrodes and avoids the need for individual wired connections and multi-potentiostats.

The early detection of disease biomarkers is associated with improved patient outcomes and improved quality of life years. The clinical sensitivity (true positive rate, individual has disease) and clinical specificity (true negative rate, individual does not have disease) of some biomarkers, such as prostate-specific antigen (PSA) does not allow them to make a definitive diagnosis. However, the ability to conveniently, e.g., in a patient's home, monitor change, in their concentration over time could represent a step change in contemporary medicine especially when populations are becoming older. PSA has been detected with wireless ECL.[22] For example, using gold nanoclusters functionalised with 6-aza-2-thiothymine as the luminophore. In an antibody sandwich assay, the binding of a cerium

oxide-poly(ethylenimine) composite functionalised with a secondary antibody triggers energy transfer quenching of the ECL. The linear dynamic range is from 1×10^{-5} ng/mL to 200 ng/mL and a LOD of 2.2 fg/mL is reported. Cytokeratin 19 fragment 21-1 (CYFRA 21-1), which is an emerging effective biomarker of lung cancer, has also been detected using a similar bipolar electrochemiluminescence, BPECL, strategy at concentrations from 10 fg/mL to 100 ng/ml.[23]

The concentration of alkaline phosphatase, ALP, in serum can be a valuable tumour marker with high specificity for cancers such as liver and sarcomas, especially osteosarcoma. The ability to measure biomarker concentrations at increasingly lower levels has the promise of earlier disease detection, but many BPECL systems achieve LODs in the µM range and there is a need for greater sensitivity. Figure 3 illustrates an attractive strategy for enhanced analytical performance developed by Zhang and co-workers.[24] When an appropriate voltage is applied to the feeder electrodes, a complete electrochemical cell is generated through electron and ion transfer in solution. The ALP catalysed the conversion of p-APP to 4-aminophenol (p-AP) which was then oxidised at the anode of the BPE leading to ECL at the anode of the driving electrode. Thus, ALP was detected through the oxidation reaction of p-AP ultimately leading to ECL generation.

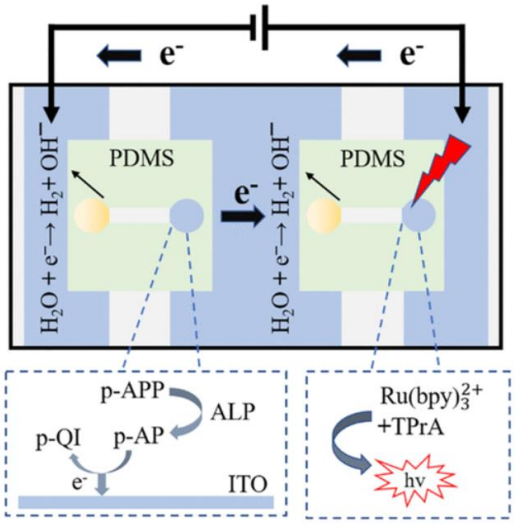

Figure 3. *Electrochemiluminescence detection of ALP based on a closed bipolar cell. Reproduced from Yang, X.-Y.; Bai, Y.-Y.; Huangfu, Y.-Y.; Guo, W.-J.; Yang, Y.-J.; Pang, D.-W.; Zhang, Z.-L.; Ultrasensitive Electrochemiluminescence Biosensor Based on Closed Bipolar Electrode for Alkaline Phosphatase Detection in Single Liver Cancer Cell, Anal. Chem. 2022, 93, 1757-1763, DOI: 10.1021/acs.analchem.0c04517*

The analytical performance is excellent with signal amplification of approximately 1000-fold compared to conventional strategies leading to an attomolar LOD. ALP could be detected in different types of

cells, e.g., single Hep G2 cells which could have significant benefits for understanding heterogeneity in (cancer) cell populations. Other "small molecule" biomarkers that have been detected using BPECL include tryptamine.[25]

An attractive strategy for the rapid development of sample-to-answer devices is to combine 3D printing and smartphone camera detection within a bipolar ECL system. For example, Goel and co-workers[26] developed a six-well 3D-printed closed bipolar ECL for the detection of glucose and choline using luminol/peroxide-based enzymatic reactions. A smartphone camera was used to image the ECL emission from which the concentration-dependent ECL intensities could be extracted, as well as using the phone to power the system. The dynamic range was from 0.1 to 10 mM for glucose and 0.1 to 5 mM choline, with LODs of 24 µM and 10 µM, respectively. Preliminary spiking measurements in blood serum suggest significant point-of-care potential for the device, especially for low-resource environments.

Bipolar ECL has also been applied to the detection of biological cells which has important implications for disease detection, e.g., circulating cancer tumour cells and sepsis causing bacterial infections. For example, a nanocomposite comprising luminol-chitosan-platinum nanoparticles has been combined with an aptamer that binds selectively to B lymphoma cells to enable their rapid detection at concentrations as low as 31 cells/mL.[27] BPECL has also been developed as a powerful tool for investigating living cells. For example, as shown in Figure 4, Sojic and co-workers demonstrated the measurement of intracellular hydrogen peroxide, glucose as well as the sphingomyelinase activity.[28] Their elegant strategy involves a nanopipette tip where the walls are functionalised with platinum that is used as an open bipolar ECL device to achieve intracellular wireless electroanalysis. The combination of the nanopipette geometry and the bipolar ECL generation leads to spatially confined ECL emission from luminol. The porosity of the platinum deposit allows intracellular molecules to move into the nanopipette that are then coupled to enzymatic reactions. Significantly, when compared to classical geometries this device operates at a remarkably low potential thus minimizing the prospect of the voltage influencing cellular activity.

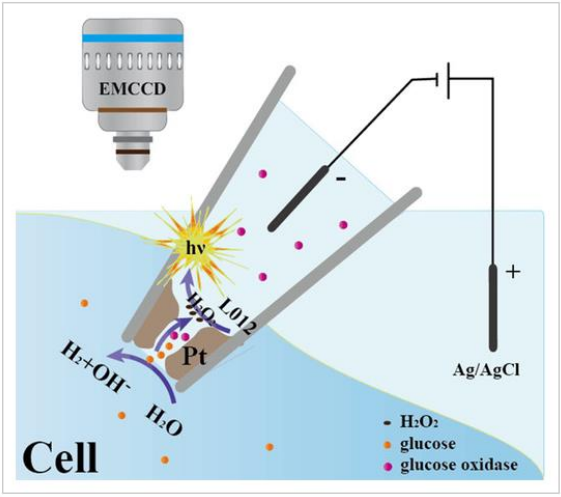

Figure 4. *Representation of the bipolar ECL detection at the porous Pt deposit inside a nanopipette, which is inserted into the cytosol for intracellular wireless electroanalysis. Reproduced from Wang, Y.; Jin, R.; Sojic, N.; Dechen Jiang, D.; Chen, H.-Y.; Intracellular Wireless Analysis of Single Cells by Bipolar Electrochemiluminescence Confined in a Nanopipette, Angew. Chem. Int. Ed.,* ***2020****, 132(26), 10502-10506, DOI: 10.1002/ange.202002323.*

The ECL intensity correlates with the concentration of glucose between 0.1 and 10 mm with an LOD of 0.1 mm which effectively addresses the physiologically relevant range. More significantly, in agreement with results averaged over many cells, measurements on *single* living HeLa cells indicated a hydrogen peroxide concentration of 4±3 mM.

BPECL has been developed into a distinct branch of microscopy and applied to biological cells to image biological cells and even sub-cellular structures.[29]

4. Electrodeposition of (Nano)Materials. The formation of thin films and nanomaterials using instrumental and chemical methods is pivotal to diverse health-related challenges from sensors for biomarker detection to on demand drug release systems and electroceutical platforms for the electrical and electrochemical stimulation of cells and tissue.

Conducting polymers play a central role in all of these for health-oriented applications and as shown in Figure 5, the ability to control the thickness, morphology, biocompatibility and stability of thin films is particularly important. Electrodeposition using conventional 3-electrode cells allows *uniform* films of conducting polymers to be deposited and when templates, e.g., 2D and 3D arrays of particles (nanosphere lithography), are used, shaped conducting polymer (CP) films/3D structures and (nano)wires can be created.[30] Significantly, *wireless* electrochemistry allows films with both thickness

and composition gradients to be created on diverse bipolar electrode materials and shapes from plates to spherical nanoparticles and 3D-printed scaffolds.[31] If the potential-dependent rate of heterogeneous electron transfer influences the rate of film formation, then for a fixed electrodeposition time, the film thickness is different for different locations on the electrode because the potential is not uniform across the BPE surface. Moreover, its "*as synthesised*" redox composition, and perhaps its morphology (due to different deposition rates) will vary across the surface. These variations could be used as a kind of "*2D barcode*" to quickly identify the optimum thickness, chemical composition and redox state for a given application, e.g., sensors, drug release systems, cell culture surfaces and valving in microfluidic systems. In addition, Figure 6 shows that complex CP branching patterns may be formed without the use of a template.[32] Additionally, dendrite-inspired CP fibres form at both terminals of a BPE by using AC-bipolar electropolymerisation. This AC approach periodically swaps the anode and cathode giving very different materials compared to DC fields. It provides an excellent demonstration of the direct connection between the electric field distribution in space and time and the materials properties. It also shows how novel materials with different thicknesses, redox compositions and structures, e.g., porosity as controlled by the deposition rate, can be created using bipolar electrochemistry.

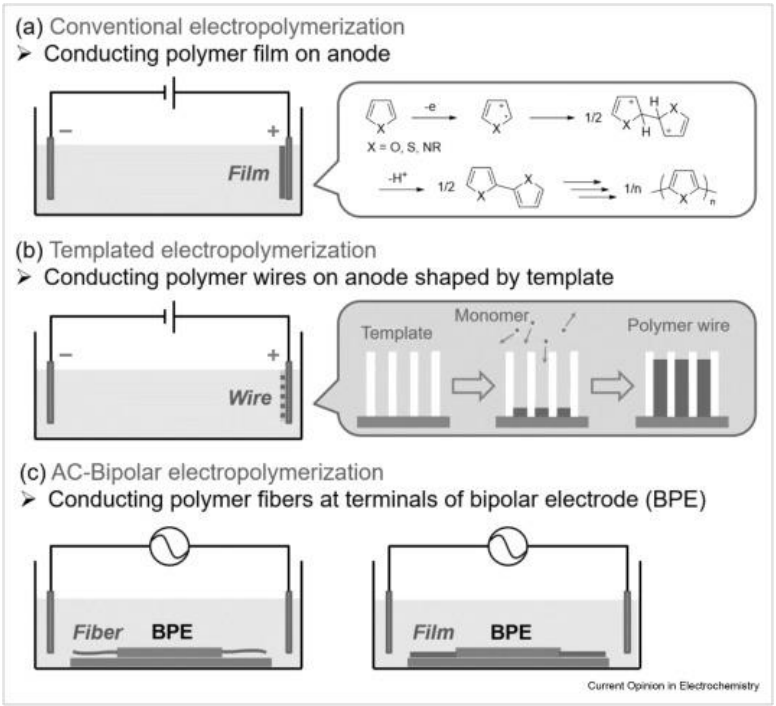

Figure 5. a) *Deposition of a conducting polymer film on the surface of the wired anodic feeder electrode using electrically induced chemical oxidation and subsequent polymerization of the monomer species in an electrolyte solution.* ***b)*** *Formation of conducting polymer wires spatially dictated by an inert template located on the anodic feeder electrode surface.* ***c)*** *Schematic illustration of fibre-conducting polymer depositions (left) and film deposition (right) at the anodic terminal of the immersed wire-free bipolar electrode (BPE) facilitated by the*

modified electric field housed by the wired feeder electrodes. Reproduced from Chen, Z.; Villani, E.; Inagi, S. Recent Progress in Bipolar Electropolymerization Methods toward One-Dimensional Conducting Polymer Structures. Curr. Opin. Electrochem. ***2021****, 28, 100702. DOI:10.1016/j.coelec.2021.100702.*

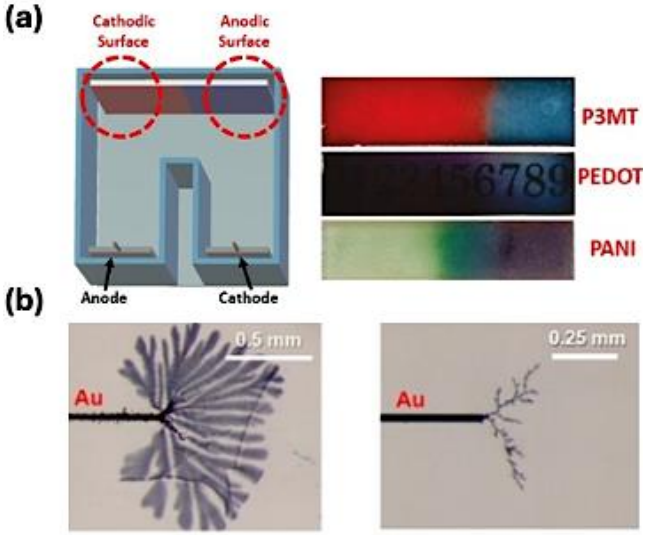

Figure 6. a) *A U-shaped bipolar cell with split anode and cathode feeder electrode placed opposite a BPE platform all immersed in monomer-electrolyte solution (left) and optical images of the resulting doped gradient CP films of Poly(3-methylthiophene), PEDOT and PANI following the application of an applied voltage (right).* ***b)*** *Optical images of PEDOT film (right) and PEDOT fiber (left) at different frequencies 5Hz and 50Hz respectively, originating from the anodic terminal of a gold BPE nanotube. Reproduced from Watanabe, T.; Ohira, M.; Koizumi, Y.; Nishiyama, H.; Tomita, I.; Inagi, S.; In-Plane Growth of Poly(3,4-ethylenedioxythiophene) Films on a Substrate Surface by Bipolar Electropolymerization, ACS Macro Lett.* ***2018****, 7(5), 551–555. DOI:10.1021/acsmacrolett.8b00170.*

From a production standpoint, it is significantly easier to produce large numbers of films using BPE since multiple bipolar electrodes can be immersed in parallel between a single pair of feeder electrodes without the need for dedicated, individual interconnects allowing many identical coatings to be produced simultaneously.

5. Wire-free Release of Active Pharmaceutical Ingredients. Healthcare is moving away from blockbuster drugs and a 'one-size fits all' approach to personalised medicine where drug selection and dosage are based on an individual's unique genome, metabolism, and immune response. There are significant opportunities for advanced Drug Delivery Systems (DDS) that can release APIs on demand, ideally informed by a sensor-based measurement of the systemic concentration for closed-loop control. These systems could avoid the cumulative and life-threatening side effects of some therapies (it is estimated that there are more than 200,000 deaths annually in the EU due to side effects of medicines costing more than €80 billion annually). Some electrodeposited CPs are highly

biocompatible and can be loaded with APIs that can be effectively released by oxidising the film. The total loading depends on the quantity of CP deposited and the release kinetics are highly sensitive to the CP composition, the micro- and nano-scale structure of the layer (influenced by the electrodeposition conditions), and the oxidation state of the polymer film.[33] Wirefree electrochemistry has attractive properties for the electrodeposition of the CP-based DDS, e.g., the ability to generate films with mixed chemical composition/structure and different drug loadings along their length, as well as Janus drug-loaded particles. Also, from the perspective of release, they offer the possibility of achieving different API release rates along their length because of a different structure or the potential gradient that is established by the feeders. These properties could improve the outcome of cancer patients, e.g., by delivering a high dose of an antineoplastic drug close to the centre of a tumour and a lower concentration further away to reduce side effects. The ability to deliver a drug locally, e.g., miRNA, or neuro-growth factors in the brain to treat neurodegenerative conditions such as Parkinson's, Alzheimer's and Huntington's and overcome the blood–brain barrier is likely to be especially impactful. Effective wireless release of a neuro-growth factor, brain-derived neurotrophic factor (BDNF) was successfully demonstrated by Qin and co-workers[34] whereby the BNDF particles embedded in a PPy-PMAS conducting polymer film were released following the application of wireless bipolar electrical stimulation, this led to enhanced neurite outgrowth of human neuroblastoma (SH-SY5Y) cells.

4. Electrostimulation of Biological Cells: The implantation of cells represents a significant emerging therapeutic intervention to treat diseases ranging from diabetes to neurodegeneration and nerve cell regrowth. It has become increasingly clear that electrochemical processes play a key role in many physiological and biochemical processes from nerve impulse transmission and mediating electrolyte balance to enabling antioxidant defence mechanisms and acting as a driving force for metabolic pathways and redox signalling. The ability to manipulate cellular responses and invoke phenotypic alterations of target cells through electrochemical stimulation is of utmost importance, not only for elucidating disease mechanisms, but also to more precisely mimic biological systems and to optimise the performance of implantable bioelectronic devices.[35] Cell stimulation can drive cell proliferation, differentiation and interconnection of nerve-related cells. Bipolar electrochemical stimulation, BPES, allows cells immobilised on a conducting platform to be stimulated wirelessly with potentials whose spatial and temporal properties can be controlled. Electronically conducting polymers (CP) are very attractive for the creation of biocompatible, implantable devices and have proven useful in tissue engineering and controlled drug release systems.[33] A particularly important material is poly(3,4-ethylene dioxythiophene) (PEDOT) that can be doped with a diverse range of synthetic or biological

counter-ions, with the most common being polystyrene sulfonate (PSS).[36] PEDOT was used in the very first coated neural probes in 2003[37] and the first PEDOT electrodes were placed in the human brain approximately a decade ago.[38] A significant challenge for translating implantable devices into clinical practice is FDA approval but this was successfully achieved for PEDOT in 2016 through the 'Amplicoat', technology and there is good reason to be optimistic about other CPs in the future.

4.1 Bipolar Electrochemical Stimulation - *in vitro*: As shown in Figure 7, Qin et al. demonstrated effective bipolar electrical stimulation of PC 12 nerve cells embedded on soft (free-standing) PPy-PMAS-collagen/PEDOT-PSS films.[39] Intermittent, wire-free electrostimulation over a week dramatically increased the total number of cells alongside a notable increase in both neurite length and interconnectivity leading to the formation of complex neural networks.

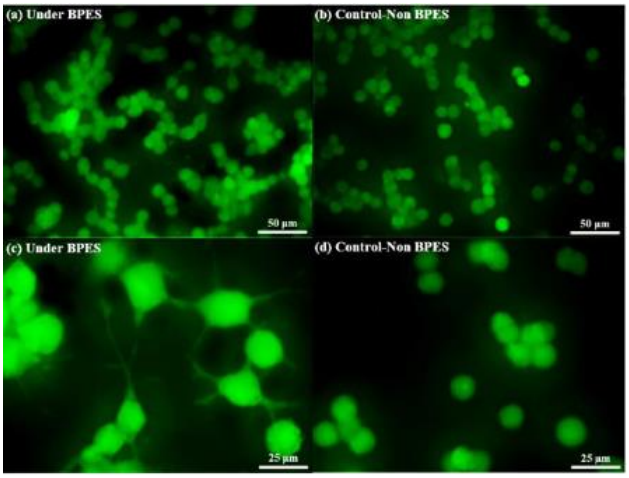

Figure 7. (a) *Fluorescent images on Day 7 via live/dead assay using calcein AM (green:live) and PI(red:dead) staining method of PC 12 clusters embedded on PPy-PMAS-DS/collagen under BPES, displaying increased cell number and neural neurite growth.* ***(b)*** *Fluorescent images on Day 7 of the PPy-PMAS-DS/collagen platform without BPES implementation are to be used as a control sample for cell number and neurite growth comparison.* ***(c)*** *Fluorescent image Day 7 of PC 12 cells showcasing extensive neurite growth/branching induced through BPES.* ***(d)*** *Fluorescent image Day 7 of undifferentiated PC 12 cells through the absence of BPES. Reproduced from Qin, C.; Yue, Z.; Huang, X.-F.; Forster, R. J.; Wallace, G. G.; Chen, J. Enhanced Wireless Cell Stimulation Using Soft and Improved Bipolar Electroactive Conducting Polymer Templates. App. Mat. Today 2022, 27, 101481. DOI:10.1016/j.apmt.2022.101481.*

Cells tend to inherit particular genotype/phenotype characteristics to effectively perform their desired function. For example, RBCs have a biconcave disc shape to increase the available surface area and optimize oxygen and CO_2 uptake. These characteristics may be enhanced or altered through a multitude of physical and chemical-related cues, such as electrochemical stimulation. Shifting from 2D bipolar stimulation platforms (e.g. planar electrodes coated with conducting polymers) to complex 3D

bio-mimetic structures could allow accurate physiological architectures to be created that replicate *in vivo* cellular behaviours.

4.2 Biomimetic 3D Architectures: Rawson and co-workers developed a novel composite material consisting of pentaerythritol triacrylate (PETrA) and multiwalled carbon nanotubes (MWCNTs).[40] This biocompatible material was 3D printed into a bio-inspired structure of stacked myofibrils for incorporation of human-induced stem cell-derived cardiomyocytes (hPSC-CMs). As illustrated in Figure 8, the effects of the physical structure/topography, its chemical composition and the effects of wireless electrical stimulation were investigated. PETrA and composite materials promote hPSC-CMs maturation and organisation, but more importantly, the 3D architecture further amplified this effect. The coupling of wireless electrochemical stimulation with 3D anatomically correct structures not only enhances cell stimulation but presents a unique opportunity to develop bio-inspired bioelectronics. Biomimetic platforms, if integrated successfully, could offer synergistic effects regarding efficient cell stimulation and combating rejection issues of implants aided by their unique design.

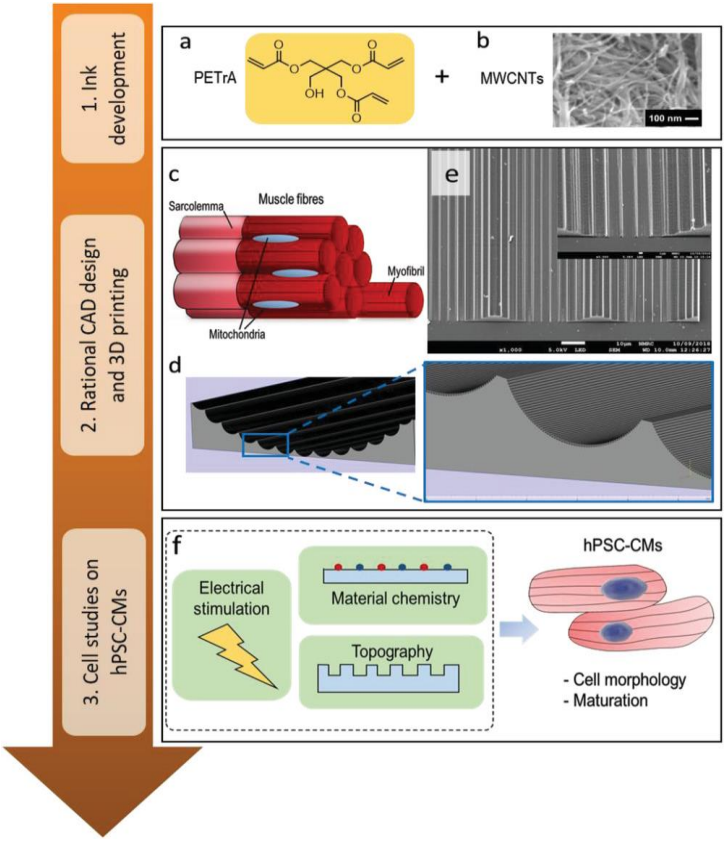

Figure 8. *Processes involved in ink development, 3D printing and stimulation of human-induced stem cell-derived cardiomyocytes.* ***1)*** *Biocompatible ink material was comprised of both* ***a)*** *pentaerythritol (PETrA) and* ***b)*** *multi-walled carbon nanotubes (MWCNTs).* ***2)*** *3D printed structure impaired by* ***c)*** *in vivo structure of stacked myofibrils designed using* ***d)*** *CAD modelling and characterised through* ***e)*** *SEM-imaging. Reproduced from Vaithilingam, J.; Sanjuan-Alberte, P.; Campora, S.; Rance, G. A.; Jiang, L.; Thorpe, J.; Burroughs, L.; Tuck, C. J.;*

Denning, C.; Wildman, R. D.; Hague, R. J. M.; Alexander, M. R.; Rawson, F. J. Multifunctional Bioinstructive 3D Architectures to Modulate Cellular Behavior. Adv. Func. Mats. ***2019****, 29 (38), 1902016. DOI:10.1002/adfm.201902016.*

Retrospects and Prospects. Bipolar electrochemiluminescence, BPECL, has developed from a somewhat obscure and under-utilised technique 10 to 15 years ago into a cutting-edge strategy for the highly sensitive and selective electrochemical detection of disease biomarkers. Current state-of-the-art devices address diverse disease detection and diagnosis issues from low-cost point-of-care devices to measurements within single biological cells. BPECL lends itself uniquely to multianalyte detection, e.g., by placing electrodes of different lengths in a single bipolar cell, the voltage induced at the tips of each electrode depends on their length and can therefore be used to drive light-generating reactions selectively, e.g., by tuning the redox potential of the ECL luminophore. However, there remains much to be understood about bipolar systems, e.g., the spatial distribution along the bipolar electrode is increasingly recognised as not being fully described by a simple linear decay model, but is structured and time-dependent as processes, such as local ion depletion occur, e.g., due to faradaic reactions or neutralisation reactions. There are opportunities for detailed finite element modelling of the electric field distribution for even relatively simple geometries and certainly for models that integrate mass transport by diffusion *and* migration as well as the effects of heterogeneous electron transfer and the impact of the electric field on homogenous chemical reactions, e.g., the reaction of a ground state label and an electrogenerated co-reactant. Overall, there are strong reasons to believe the future is bright, the future is wirefree!

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